

Functional Assessment of Tissues with Magnetic Resonance Imaging

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Over the past ten years, magnetic resonance imaging (MRI) has rapidly progressed from a purely anatomical imaging technique to one that reports on a wide variety of tissue functions. While most of these techniques have been developed for clinical problems or animal models, it is clear that they will be useful for studying engineered tissues both *in vitro* and *in vivo*. The goal of this presentation is to introduce the wide range of anatomical and functional information that can be assessed with magnetic resonance imaging.

ANATOMY WITH MRI

The major impact of MRI on the clinical sciences has derived from its ability to obtain millimeter resolution of tissue non-invasively.¹ Indeed for almost every known pathological condition, there is an anatomical MRI technique that can give contrast to distinguish pathologic from normal tissue. Recent increases in magnetic fields and image-acquisition strategies are pushing the resolution that can be obtained with MRI: 50–100-micron resolution with *in vitro* samples and rodents in very high magnetic fields (> 7T) can be routinely obtained in a few minutes and applications to engineered tissues are appearing.² In the human brain, resolution approaching 300 microns can be expected in the next few years.

MRI TO MONITOR MOTION

Since its early days, MRI has been used to monitor motion in biological samples. This range of motion goes from the macroscopic (such as ventricular dynamics of the heart) to the microscopic (e.g., diffusion of water). Specialized MRI tagging ap-

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proaches enable detailed analysis of contraction of muscle at roughly millimeter resolution.³ Diffusion MRI offers sensitivity to cellular volume and can probe the extent of anisotropy in complex media. These properties have made diffusion MRI useful for evaluating tissue damage due to stroke⁴ and to trace white matter tracts in the brain.⁵ Recent successes at labeling cells with strong, iron oxide-based contrast agents show much progress in enabling MRI to monitor cell migration in tissues.⁶

MRI TO MONITOR HEMODYNAMICS

Techniques that allow MRI to monitor tissue hemodynamics are having a large impact in assessing the function of tissues. Indeed, since assessing vascularization of engineered tissues is of major importance, these MRI techniques should have broad application. Blood volume is readily measured using MRI contrast agents that are restricted to the blood.⁷ Oxygenation of hemoglobin can be indirectly assessed using the paramagnetic properties of hemoglobin to give so-called blood oxygenation level-dependent MRI. This has been the primary tool for functional MRI of the brain.⁸ Regional blood flow can be quantitated using techniques that spin-label arterial blood.⁹ All of these techniques are being applied to a broad range of problems in physiology including tumor angiogenesis, cardiac function, and brain function. It is exciting to apply them to engineered tissues both *in vitro* and *in vivo*.

MRI TO MONITOR METABOLISM

Most MRI is based on detection of hydrogen atoms in water, although ^1H in other molecules and other nuclei such as ^{31}P (to study cellular energetics), ^{13}C (to study metabolic fluxes), ^{19}F (to study drug metabolism), and ^{23}Na (to study ion homeostasis) can be readily detected *in vivo*.¹ The major disadvantage of these techniques is their relatively limited spatial resolution (about 1 cc). There is a history of using MR spectroscopic techniques to study cellular metabolism in a variety of bioreactors that hold much potential for studying engineered tissues.¹⁰

FUNCTIONAL AND MOLECULAR SPECIFIC CONTRAST AGENTS

Contrast agents have played a large role in the clinical usefulness of MRI. Function- and molecule-specific contrast agents that are sensitive to a number of physiologic functions are being developed. These can be quite simple substances or ones that require significant chemical synthesis. For example, it is well known that manganese ion can enter excitable cells through voltage gated calcium channels and is an excellent MRI contrast agent. These properties have been combined to use manganese to mark active regions in the rodent brain.¹¹ Interestingly, manganese also is transported in an anterograde fashion in the nervous system, making it useful for tracing neuronal connections.¹² New, so-called “smart contrast agents” are being developed whose contrast changes with a change in calcium concentration as occurs during an action potential.¹³ Finally, peptides or antibodies that bind specific molec-

ular targets can be attached to a variety of MRI contrast agents for imaging the distribution of specific membrane receptors.

Numerous other promising areas of MRI development may also have an impact on tissue engineering. For example, current density imaging holds promise for looking directly at electric fields in tissues. MRI elastography holds promise to measure the physical properties of tissues. A number of strategies for monitoring gene expression by MRI are awaiting widespread application. The rapid growth of functions that MRI can measure indicates that it should play a major role in assessing engineered tissues, *in vitro*, in animals, and in humans.

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